

## **DETAILED ACTION**

### ***Election/Restrictions***

Applicant's election with traverse of Group 1 and the species cardiac heart failure, nadolol, and beta-adrenergic receptor in the reply filed on 02/21/2008 is acknowledged. The traversal is on the ground(s) that 1) the “special technical feature is the *method for treating* a disease or condition associated with the activity of a GPCR comprising administering an inverse agonist for a G protein coupled receptor (GPCR)” and 2) there is no search burden. This is not found persuasive because a special technical feature would first have to be a common technical feature between all groups and, secondly, have to be Applicant's contribution over the prior art. In this case, what Applicant considers to be a special technical feature does not meet the first requirement of being a common technical feature between all groups. For example, Group V is directed to a composition and, therefore, lacks the method limitation required in the other groups. With regards to the search burden requirement not being met, this is not persuasive because this is not a requirement for a lack of unity finding for a 35 U.C.S. 371 national stage application.

Claims 3, 7-14 ,19, 20, 40-42, 48, 49, 52, 55, and 60 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and species, there being no allowable generic or linking claim. Applicant timely

traversed the restriction (election) requirement in the reply filed on 2/21/2008.

Accordingly, claims 1-2 and 37-39 are presented for examination

The requirement is still deemed proper and is therefore made FINAL.

### ***Specification***

The disclosure is objected to because of the following informalities: at page 75, 3<sup>rd</sup> to the last sentence of paragraph [0213], the term "tome" should be "time".

Appropriate correction is required.

### ***Claim Rejections - 35 USC § 112 - 1<sup>st</sup> – Written Description***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 37 and 38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims recite “inverse agonist for GPCR” (e.g., claim 1). There is insufficient written basis in the specification for “inverse agonist for GPCR” as a generic class.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made the invention. See, e.g., In re Wilder, 22 USPQ 369, 372-3 (Fed. Cir. 1984). (Holding that a claim was not adequately described because the specification did ‘little more than outline goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.’)

Mere indistinct terms (such as “inverse agonist for GPCR” used herein), however, may not suffice to meet the written description requirement. This is particularly true when a compound is claimed in purely functional terms. See Univ. of Rochester v. G.D. Searle, 69 USPQ 2d 1886 (CAFC 2004) at 1892, stating:

The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. A description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) described even in terms of its functioning of lessening inflammation of tissues fail to distinguish any steroid from others having the same activity or function. A description of what a material does rather than of what it is, usually does not suffice. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. (Emphasis Added).

A description of a chemical genus will usually comprise a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. See Univ. of Cali. v. Eli Lilly, 43 USPQ 2d 1398, 1406 (Fed. Cir. 1997). This is analogous to enablement of a genus under §112, ¶ 1, by showing the enablement of a representative number of species within a genus.

A chemical genus can be adequately described if the disclosure presents a sufficient number of representative species that are encompassed by the genus. If the genus has substantial variance, the disclosure must describe a sufficient number of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not specifically define what constitutes a representative number of species, the courts have indicated what does not constitute same. See, e.g., In re Gostelli, 10 USPQ 2d 1614, 1618 (Fed. Cir. 1989), holding that the disclosure of two chemical compounds within a subgenus did not adequately describe such subgenus.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the application. These include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient. MPEP 2163.

In this case, the speciation does not provide a reasonably representative disclosure of useful “inverse agonist for GPCR” – generally, a potentially huge genus inclusive of many different compounds having widely divergent structures and functions.

Claims 1-2, and 37-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

***Claim Rejections - 35 USC § 112 - 1<sup>st</sup> – Enablement***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2 and 37-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant claims a method for treat a disease or condition associated with the activity of a G protein coupled receptor (GPCR) comprising administering an inverse agonist. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The test of enablement requires a determination of whether the disclosure, when

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filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. That standard is still the one to be applied. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term “undue experimentation,” it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

**1. State and predictability of the art, and relative skill level:**

Although the skill is high in the pharmaceutical art, a disease or condition associated with the activity of a G protein coupled receptor (GPCR) was not, at the time the invention was made, at the point at which it can be treated by administering an GPCR inverse agonist. The state of the art is such that treatment of such diseases is very unpredictable; for example, even agents specific to one GPCR disease, e.g., asthma, do not function consistently. See, for instance, M. Wehling (Herz. 2002 Aug;27 Suppl 1:16-25), which teaches that asthma – a disease or condition associated with GPCR activity, was known to be contraindicated for certain specific inverse agonists, namely beta agonists (i.e., a GPCR inverse agonist) treatment. See also, Prichard et al. (Blood Press. 2001;10(5-6):366-86) teach that asthma remains an important contraindication to beta-blockade.

**2. The breadth of the claims:**

The claim is very broad and inclusive of GPCR associated diseases.

**3. The amount of direction or guidance provided and the presence or absence of working examples:**

The specification provides no guidance for treating diseases other chronic asthma. The working examples disclose the treatment of asthma, but only with one specific agonist (nadalol), and not a reasonably representative set of agonists.

**4. The quantity of experimentation necessary:**

Because of the known unpredictability of the art, no one skilled in the art would accept the assertion that the instantly claimed method of treating a GPCR associated disease with an inverse agonist of GPCR is predictable. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the invention claimed in the patent a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

***Claim Rejections - 35 USC § 112- 2<sup>nd</sup> Paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The phrase "associated with" in claim 1 is a relative term which renders the claim indefinite. The phrase "associated with" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The degree of "association" is not specified in the specification; it is not clear how closely "associated with" and in what way it is "associated with" activity of GPCR receptors a given disease or condition must be to fall within the scope of the claims. Many diseases or conditions could be "associated" with the primary disease, but the degree of "association" could vary widely depending on how the term was defined.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 37 and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Vanderhoff et al. (Am Fam Physician. 1998 Nov 1;58(7):1627-34, 1641-2).

The reference teaches long term treatment of CHF with beta blockers, such as carvedilol, an inverse agonist for the GPCR. See the paragraph bridging pages 2 and 3 of the attached reference. Table 3, at page 6 of 10, teaches a titration method of administering the drug. It teaches a starting dose of 3.125 mg bid for 2 weeks, then, if tolerated well by the patient, the amount is doubled every 2 weeks to a maximum tolerable dosage amount.

The increase in the population of  $\beta_2$ -adrenergic receptors and the sustained level of drug in the blood are inherent outcomes with such long term beneficial treatment of CHF using beta agonists.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

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2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Vanderhoff et al. (Am Fam Physician. 1998 Nov 1;58(7):1627-34, 1641-2) in view of USP 6,159,500.

The primary reference discloses as outlined above. The reference does not expressly teach the beta-blocker, nadolol. However, the secondary reference clearly discloses that nadolol is already known to be effective in treating CHF ('500, col. 23, lines 54-60). The secondary reference does not expressly teach administering nadolol in an amount or period of time that would cause an increase in the population of GPCRs.

Generally, it is prima facie obvious to select a known material for incorporation into a composition, based on its recognized suitability for its intended purpose. See Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). See also In re Leshin, 227 F.2d 197, 125 USPQ 416 (CCPA 1960). Accordingly, it would have been obvious to replace the beta blocker in the primary reference, carvedilol, with another one, nadolol, known to be useful in treating the same disease, CHF.

It would have been obvious to the skilled artisan to use another beta blocker (e.g., nadolol) known to be useful in the treatment of CHF besides the one explicitly taught in the primary reference. The skilled artisan would have been motivated by the reasonable expectation of success that nadolol would be useful in treating CHF.

### ***Conclusion***

No claims are allowed.

The following is pertinent art not relied upon for anticipatory or obviousness analysis for the current action:

- Papadoyannis et al. (Eur J Clin Pharmacol (1982) 22:487-489)
- Sproat et al. (The Annals of Pharmacotherapy (1991) 25(9):962-71).

### ***Correspondence***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRIS E. SIMMONS whose telephone number is (571)272-9065. The examiner can normally be reached on Monday - Friday from 7:30 - 5:00 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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